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THE INFLUENCE OF HYDROGEN BONDING ON THE SOLVOLYTIC REACTIVITY OF NICOTINATES IN FLUORINATED ALCOHOLS

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Abstract - A systematic investigation of solvolytic reactivities of allylic and benzylic nicotinates and their N-methylated derivatives in 80% EtOH, 97% TFE and 97% HFIP was undertaken. The nicotinates in 97% HFIP are slightly more reactive than the corresponding p-nitrobenzoates, whereas the ratio of these reactivities is inverse in 80% EtOH and 97% TFE. This observation was explained by the stronger hydrogen bonding of HFIP with nicotinate leaving group than with the p-nitrobenzoate group, which is in keeping with the larger basicity of the former comparing with the latter group. N-Methylnicotinyl esters under the same conditions show approximately 50 times greater solvolytic reactivities than the corresponding p-nitrobenzoates. These relative reactivities are insensitive to the hydrogen bonding ability of the solvent. The UV and IR spectroscopic parameters of ethyl nicotinate and ethyl p-nitrobenzoate in fluorinated alcohols are fully consistent with this observation.

The effect of solvent on nucleophilic substitution reactions has been extensively investigated.[1] This effect has been ascribed mostly to solvent polarity, its ionizing power, nucleophilicity, solvating ability, and protic vs. aprotic character. Our recent investigations of solvolytic reactions in fluorinated alcohols[2] showed the significance of an additional solvent effect, namely the ability of these fluorinated solvents to form hydrogen bonds with leaving groups which possess hydrogen-accepting ability.

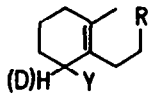
In this paper we report on solvolysis rate effects caused by interactions between fluorinated alcohols used as solvents and various nicotinates (3-pyridinecarboxylates), their N-methylated pyridinium derivatives, and p-nitrobenzoates as bases. Similar interactions were previously observed[3-5] in alkaline hydrolysis of ethyl nicotinate in dimethylsulfoxide (DMSO). The increased solvation of this ester by DMSO (compared with EtOH as solvent) was explained by the interaction between the positive end of the sulfoxide dipole in DMSO and the lone pair on the

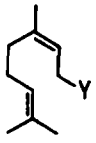
ring nitrogen. The ^{1}H NMR data[3] of this ester in DMSO, $CHCl_3$, and CCl_4 are consistent with the existence of such interactions.

The nicotinate group, introduced in this study as the leaving group in the solvolysis of allylic and benzylic substrates, possesses important advantages over the p-nitrobenzoate leaving group which was previously used in such investigations.[2,6] Whereas the solvolytic reactivity of nicotinates significantly increases upon N-alkylation[7], protonation, or even formation of hydrogen bonds with acids, the analogous p-nitrobenzoates are not so prone to these reactions and their solvolytic reactivity remains low. Furthermore, while the solubility of ordinary p-nitrobenzoates in water is negligible, nicotinates upon N-alkylation become fairly soluble in water enabling the study of bioorganic reaction mechanisms in aqueous solutions. In our recent work[8] the hydrolysis of N-methylnicotinyl esters was investigated under micellar conditions, and various modes of micelles formed with these esters and aqueous sodium dodecylsulfonate solutions were studied by ^{1}H NMR.

RESULTS AND DISCUSSION

Nicotinates 1a - 9a were prepared according to the previously described procedure[2,6] for the synthesis of p-nitrobenzoates 1c - 6c. The resulting nicotinates were also converted with methyl iodide to the corresponding N-methylpyridinium derivatives 1b - 9b.





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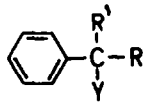


1, R = CH_2CH_3 4, R = $OCH_2C_6H_5$

2, R = $CH{=}CH_2$ 5, R = CH_2OCH_3

3, R = OCH_3 6, R = $CH_2OCH_2C_6H_5$

8, R = C_6H_5; R' = H

9, R = R' = CH_3

a, Y = ONIC (HONIC = 3-pyridinecarboxylic acid, nicotinic acid)

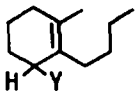
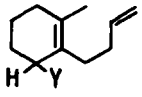
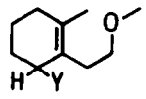
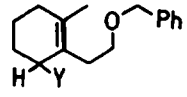
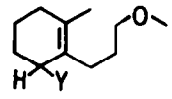
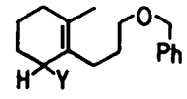
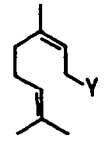
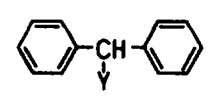
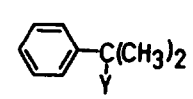
b, Y = ONMI (HONMI = 3-carboxyl-1-methylpyridinium iodide)

c, Y = OPNB (HOPNB = p-nitrobenzoic acid)

All esters 1 - 9 were solvolyzed in 80 vol % EtOH, 97 wt % CF_3CH_2OH (TFE), and 97 wt % $(CF_3)_2CHOH$ (HFIP). The rates were measured potentiometrically at a constant pH. Clear first-order kinetic behavior was observed in all cases. The kinetic results are presented in Table I.

Our previous investigations[2,6] showed that the p-nitrobenzoates 1c - 6c solvolyzed in 80% EtOH and 97% TFE via a stepwise mechanism which includes the rate-determining formation of an allylic cation as a reaction intermediate. The normal values of secondary α-deuterium kinetic isotope effects[9] obtained in the solvolysis of those esters are in keeping with the proposed reaction mechanism.[10] For the solvolysis of both the nicotinates 1a - 9a and their N-methylated pyridinium analogs 1b - 9b, and in all the solvents studied, the normal values of secondary α-deuterium isotope effects were again obtained (k_H/k_D = 1.20 - 1.27) confirming the uniformity of solvolysis mechanism for all esters 1 - 9.[10] All these esters solvolyze with the heterolysis of alkyl-oxygen bond, and not with the alternative acyl-oxygen mode of cleavage which usually occurs in natural processes.[11]

Table I. Rate Constants in Solvolysis of Esters 1 - 9

Ester	Solvent[a]	t, °C	k^b, s^{-1} Y = ONIC	Y = ONMI	Y = OPNB
1 	80 E	50	$1.37(1)\times10^{-4}$	$1.55(2)\times10^{-2}$	$2.94(1)\times10^{-4}$[c,d]
	97 T	25	$1.66(1)\times10^{-3}$	$1.01(5)\times10^{-1}$	$1.879(6)\times10^{-3}$[c]
	97 H	20	$8.65(9)\times10^{-2}$	-	$7.37(7)\times10^{-2}$[d]
2 	80 E	50	$1.13(2)\times10^{-4}$	$1.41(2)\times10^{-2}$	$2.49(2)\times10^{-4}$[c]
	97 T	25	$9.86(5)\times10^{-4}$	$6.16(7)\times10^{-2}$	$1.140(3)\times10^{-3}$[c]
	97 H	20	$3.56(3)\times10^{-3}$	-	$2.97(3)\times10^{-3}$
3 	80 E	50	$1.04(2)\times10^{-4}$	$1.24(1)\times10^{-2}$	$2.30(2)\times10^{-4}$[d]
	97 T	25	$1.88(2)\times10^{-4}$	$1.17(1)\times10^{-2}$	$2.21(1)\times10^{-4}$[d,e]
	97 H	20	$7.62(8)\times10^{-3}$	-	$6.38(7)\times10^{-3}$[d]
4 	80 E	50	$0.86(1)\times10^{-4}$	$1.02(1)\times10^{-2}$	$1.86(2)\times10^{-4}$[e]
	97 T	25	$2.20(1)\times10^{-4}$	$1.30(3)\times10^{-2}$	$2.51(2)\times10^{-4}$[e]
	97 H	20	$6.91(5)\times10^{-3}$	-	$5.81(4)\times10^{-3}$
5 	80 E	50	$1.33(1)\times10^{-4}$	$1.50(1)\times10^{-2}$	$2.956(7)\times10^{-4}$[e]
	97 T	25	$3.61(2)\times10^{-4}$	$2.36(2)\times10^{-2}$	$4.145(7)\times10^{-4}$[e]
	97 H	20	$2.21(2)\times10^{-2}$	-	$1.84(1)\times10^{-2}$
6 	80 E	50	$1.17(1)\times10^{-4}$	$1.44(3)\times10^{-2}$	$2.68(2)\times10^{-4}$[e]
	97 T	25	$4.01(3)\times10^{-4}$	$2.64(4)\times10^{-2}$	$4.72(2)\times10^{-4}$[e]
	97 H	20	$1.63(1)\times10^{-2}$	-	$1.37(1)\times10^{-2}$
7 	80 E	75	$5.81(5)\times10^{-7}$	$6.38(4)\times10^{-5}$	$1.25(4)\times10^{-6}$
	97 T	70	$0.79(1)\times10^{-5}$	$5.12(5)\times10^{-4}$	$0.93(2)\times10^{-5}$
	97 H	60	$2.71(2)\times10^{-4}$	$1.20(1)\times10^{-2}$	$2.24(2)\times10^{-4}$
8 	80 E	70	$3.45(9)\times10^{-6}$	$3.62(1)\times10^{-4}$	$7.79(9)\times10^{-6}$
	97 T	60	$2.84(2)\times10^{-5}$	$1.72(1)\times10^{-3}$	$3.30(2)\times10^{-5}$
	97 H	60	$4.73(2)\times10^{-4}$	$2.03(2)\times10^{-2}$	$3.99(5)\times10^{-4}$
9 	80 E	70	$0.67(1)\times10^{-4}$	$7.63(1)\times10^{-3}$	$1.44(3)\times10^{-4}$
	97 T	60	$6.85(4)\times10^{-4}$	$4.84(9)\times10^{-2}$	$8.12(3)\times10^{-4}$
	97 H	60	$2.35(2)\times10^{-2}$	-	$1.97(3)\times10^{-2}$

[a] 80 E is 80 vol % aqueous EtOH, 97 T is 97 wt % aqueous CF_3CH_2OH, and 97 H is 97 wt % aqueous $(CF_3)_2CHOH$.

[b] Numbers in parenthesis are uncertainties of the last reported figure, i.e., 1.37(1) = 1.37 ± 0.01; uncertainties are standard deviations of the mean.

[c] Reference 6.

[d] Reference 2a.

[e] Reference 2b.

Such alkyl-oxygen bond cleavage is common in esters which can give stable carbocations.

The ratios of solvolytic reactivity of nicotinates 1a - 9a, as well as their N-methylated pyridinium derivatives 1b - 9b, and the corresponding p-nitrobenzoates 1c - 9c (defined as k(RONIC)/k(ROPNB) and k(RONMI)/k(ROPNB) ratios) show remarkably small variation with the structural changes in group R for a particular solvent (Table II). However, the k(RONIC)/1(ROPNB) ratio changes significantly with solvent; it is the smallest (0.44-0.47) in 80% EtOH, medium (0.84-0.88) in 97% TFE,

Table II. Leaving Group Rate Ratios in Solvolyses of Esters 1 - 9.

Ester	k(RONIC)/k(ROPNB)			k(RONMI)/k(ROPNB)		
	80 E	97 T	97 H	80 E	97 T	97 H
1	0.47(1)[a]	0.88(1)[d]	1.17(2)[f]	53[a]	54[d]	-
2	0.45(1)[a]	0.86(1)[d]	1.20(2)[f]	57[a]	54[d]	-
3	0.45(1)[a]	0.85(1)[d]	1.19(2)[f]	54[a]	53[d]	-
4	0.46(1)[a]	0.88(1)[d]	1.19(1)[f]	55[a]	52[d]	-
5	0.45(1)[a]	0.87(1)[d]	1.20(1)[f]	51[a]	57[d]	-
6	0.44(1)[a]	0.85(1)[d]	1.19(1)[f]	54[a]	56[d]	-
7	0.46(2)[b]	0.85(2)[c]	1.21(2)[e]	51[b]	55[c]	54[e]
8	0.44(1)[c]	0.86(1)[e]	1.19(2)[e]	46[c]	52[e]	51[e]
9	0.47(1)[c]	0.84(1)[e]	1.19(2)[e]	53[c]	59[e]	-

[a]At 50°C. [b]At 75°C. [c]At 70°C. [d]At 25°C. [e]At 60°C. [f]At 20°C.

and the largest (1.17-1.20) in 97% HFIP. These differences can be ascribed to the formation of hydrogen bonding between the alcohols used as solvents, and the leaving groups of esters acting as hydrogen acceptors.[12] The strength of such hyrogen-bonding interactions depends on the acidity of alcohol and the hydrogen-accepting ability of the basic part of the ester.

It is known[7] that methyl N-methylnicotinate hydrolyzes about 100 times faster that methyl nicotinate due to the larger positive charge in the aromatic ring of the former ester relative to that of the latter. Therefore, the observed increase in solvolytic reactivity of nicotinates 1a - 9a (relative to that of the corresponding p- nitrobenzoates 1c - 9c) in fluorinated alcohols can be explained by an increase of the positive charge on the nicotinate group due to pronounced hydrogen-bonding interactions. These interactions are stronger with the nicotinate than with the p-nitrobenzoate leaving group because of the larger basicity of the former. The most pronounced differences between the nicotinates 1a - 9a and p-nitrobenzoates 1b - 9b in hydrogen-bonding interactions appear with 97% HFIP, being the strongest acid among the alcohols used.

In the case of N-methylpyridinium derivatives 1b - 9b (where the heterocyclic ring has large positive charge) the basicity of pyridinium moiety is much smaller that that of pyridinyl group in nicotinates 1a - 9a. Therefore the ability of pyridinium esters 1b - 9b to form hydrogen bonds with fluorinated alcohols is very small: it is similar to that of p-nitrobenzoates 1c - 9c, but almost negligible when compared with that of nicotinates 1a - 9a. The ratio k(RONMI)/k(ROPNB) is virtually the same (∿50) with all solvents studied. Thus the solvolytic reactivity of nicotinates significantly increases upon methylation of a heterocyclic nitrogen, but then becomes insensitive to a hydrogen-bonding effect of solvent.

These hydrogen-bonding interactions were also studied by spectroscopic methods. The UV and IR spectra of solutions of ethyl nicotinate and ethyl p-nitrobenzoate in fluorinated and fluorine-free alcohols were recorded. With HFIP and TFE as solvents, the aromatic bands in UV spectra show a hypsochromic shift and a hypochromic effect relative to the reference values of λ_{max} and ε observed with i-PrOH as a solvent (Table III) These results are fully consistent with the known[13] UV parameters of

Table III. Spectral Data of Ethyl Nicotinate and Ethyl p-Nitrobenzoate in Various Alcohols as Solvents

Solvent	Ethyl nicotinate		Ethyl p-nitrobenzoate	
	$\Delta\lambda_{max}$[a] / nm	$\Delta\nu_{max}$(C=C)[b] / cm^{-1}	$\Delta\lambda_{max}$[a] / nm	$\Delta\nu_{max}$(C=C)[b] / cm^{-1}
i-PrOH	0.0[d]	0.0[e]	0.0[f]	0.0[g]
EtOH	0.5	2.0	0.5	0.5
TFE	4.5	7.0	2.5	1.5
HFIP	7.5	13.0	3.5	2.0
HCl		40.0		2.5
Quatern.[c]		45.0		

[a] Hypsochromic shifts of aromatic band relative to the reference value of λ_{max} in i-PrOH as a solvent.

[b] Shifts of the aromatic C=C vibrational band toward larger wavenumbers relative to the reference value of ν_{max} in i-PrOH as a solvent.

[c] Data for ethyl N-methylnicotinate in KBr pellets.

[d] λ_{max} = 307.5 nm

[e] ν_{max}(C=C) 1594 cm^{-1}

[f] λ_{max} = 310.0 nm

[g] ν_{max}(C=C) 1610 cm^{-1}

protonated aromatic heterocyclic compounds. The observed hypsochromic shifts are far more intensive in the case of ethyl nicotinate than of ethyl p-nitrobenzoate, confirming the stronger hydrogen-accepting ability of the former comparing with the latter ester.

Ethyl nicotinate upon N-methylation or protonation shows in IR a large shift of the vibrational band which corresponds to the aromatic C=C bond. This band is shifted towards larger wavenumbers relative to the value for ethyl nicotinate in i-PrOH as a solvent (Table III). This result can be explained by a decrease of electronic density in the aromatic ring[13] of ethyl nicotinate upon protonation or N-methylation. A similar effect, although less pronounced, was observed in IR spectra of solutions of ethyl nicotinate in fluorinated alcohols. On the contrary, ethyl p-nitrobenzoate is almost insensible to this effect. The corresponding aromatic IR band of this ester shows very small shifts (relative to the value for sample in i-PrOH as a solvent) not only with fluorinated alcohols as solvents, but also in HCl solution.

In conclusion, our results show that the better hydrogen-accepting ability of nicotinates compared with that of p-nitrobenzoates is reflected in a greater sensitivity of their solvolytic reactivity and spectroscopic parameters to a change in hydrogen-donating ability of a solvent. Also, the reactivity of

N-methylnicotinates, being significantly higher than that of the corresponding p--nitrobenzoates, could be of special advantage in studies where solvolyses in water are to be investigated.

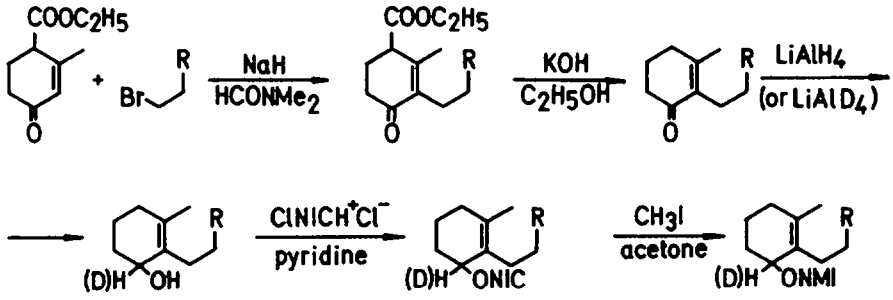
EXPERIMENTAL

Infrared spectra of samples in KBr were recorded on a Perkin-Elmer 257 Spectrometer. ^{1}H NMR spectra were recorded on a JEOL FX-90Q spectrometer. Signal positions were given in δ units, with tetramethylsilane as the internal standard. All new compounds were characterized by ^{1}H NMR and IR spectroscopy and in some cases also by elemental analysis.

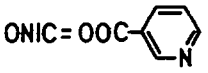
The nicotinates 7a, 8a, and 9a[8a]; N-methylnicotinates 7b-9b[8a] and p-nitrobenzoates 1c[2a], 2c[6], 3c[2a], 4c[2b], 5c[2b], 6c[2b], 8c[14], and 9c[15] were prepared and characterized as previously described.

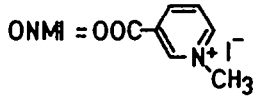
Synthesis of Compounds

Following the published procedure[8a] nicotinates 1a- 6a and N-methylnicotinates 1b-6b were prepared according to Scheme 1.



1a, R = CH_2CH_3 1b, R = CH_2CH_3
2a, R = $CH{=}CH_2$ 2b, R = $CH{=}CH_2$
3a, R = OCH_3 3b, R = OCH_3
4a, R = $OCH_2C_6H_5$ 4b, R = $OCH_2C_6H_5$
5a, R = CH_2OCH_3 5b, R = CH_2OCH_3
6a, R = $CH_2OCH_2C_6H_5$ 6b, R = $CH_2OCH_2C_6H_5$





Scheme 1

2-Butyl-3-methyl-2-cyclohexenyl Nicotinate (1aH)

Yield 92%; IR 3090, 3060, and 3040 (Ar-H), 1720 (CO-O-C), 1595 (C=C), 1285 and 1120 (C-O), 750 and 710 cm^{-1} (Ar-H); ^{1}H NMR ($CDCl_3$) δ 9.23, 8.76, 8.30 and 7.35 (4H, four m, nicotinyl), 5.50-5.70 (1H, broad s, O-CH), 1.73 (3H, s, C=C-CH_3), 0.95-2.15 (15H).

2-(3-Butenyl)-3-methyl-2-cyclohexenyl Nicotinate (2aH)

Yield 91%; IR 3080, 3060, and 3040 (Ar-H and C=C-H), 1720 (CO-O-C), 1645 and 1595 (C=C), 1282 and 1120 (C-O), 916 ($HC=CH_2$), 750 and 710 cm^{-1} (Ar-H); ^1H NMR ($CDCl_3$) δ 9.18, 8.68, 8.27, and 7.33 (4H, four m, nicotinyl), 5.80 (1H, m, C=CH), 5.50-5.70 (1H, broad s, O-CH), 4.95 (2H, m, $C=CH_2$), 1.73 (3H, s, $C=C-CH_3$), 1.40-2.30 (10H).

2-(2-Methoxyethyl)-3-methyl-2-cyclohexenyl Nicotinate (3aH)

Yield 93%; IR 3090, 3060, and 3040 (Ar-H), 1720 (CO-O-C), 1594 (C=C), 1283 and 1120 (C-O), 750 and 710 cm^{-1} (Ar-H); ^1H NMR ($CDCl_3$) δ 9.19, 8.74, 8.33 and 7.37 (4H, four m, nicotinyl), 5.50-5.70 (1H, broad s, O-CH), 3.36 (2H, t, OCH_2), 3.24 (3H, s, OCH_3), 1.76 (3H, s, $C=C-CH_3$), 1.20-2.37 (8H).

Anal. Calcd. (%) for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09
Found (%): C, 69.50; H, 7.84; N, 4.88

2-(2-Benzyloxyethyl)-3-methyl-2-cyclohexenyl Nicotinate (4aH)

Yield 91%; IR 3080, 3050, and 3030 (Ar-H), 1722 (CO-O-C), 1598 (C=C), 1295 and 1120 (C-O), 753, 712, and 692 cm^{-1} (Ar-H); ^1H NMR (CD_3OD) δ 9.18, 8.73, 8.35, and 7.37 (4H, four m, nicotinyl), 7.31 (5H, s, C_6H_5), 5.37-5.62 (1H, broad s, O-CH), 4.42 (2H, s, $ArCH_2$), 3.45 (2H, t, OCH_2CH_2). 2.41 (2H, t, OCH_2CH_2), 1.73 (3H, s, $C=C-CH_3$), 1.45-2.20 (6H).

2-(3-Methoxypropyl)-3-methyl-2-cyclohexenyl Nicotinate (5aH)

Yield 97%; IR 3090, 3060, and 3040 (Ar-H), 1720 (CO-O-C), 1596 (C=C), 1285 and 1120 (C-O), 760 and 710 cm^{-1} (Ar-H); ^1H NMR (CD_3OD) δ 9.15, 8.74, 8.35, and 7.40 (4H, four m, nicotinyl), 5.30-5,57 (1H, broad s, O-CH), 3.48 (2H, t, CH_2O), 3.41 (3H, s, OCH_3), 1.72 (3H, s, $C=C-CH_3$), 1.40-2.50 (10H).

2-(3-Benzyloxypropyl)-3-methyl-2-cyclohexenyl Nicotinate (6aH)

Yield 93%; IR 3100, 3070, and 3040 (Ar-H), 1722 (CO-O-C), 1598 (C=C), 1285 and 1125 (C-O), 752, 712, and 690 cm^{-1} (Ar-H); ^1H NMR (CD_3OD) δ 9.17, 8.73, 8.35, and 7.42 (4H, four m, nicotinyl), 7.31 (5H, s, C_6H_5), 5.35-5.60 (1H, broad s, OCH), 4.42 (2H, s, $ArCH_2$), 3.48 (2H, t, CH_2OBz), 1.73 (3H, s, $C=C-CH_3$), 1.40-2.50 (10H).

1-Methyl-3-(2-butyl-3-methyl-2-cyclohexenyloxycarbonyl)pyridinium Iodide (1bH)

Yield 91%; IR 3100, 3065, and 3040 (Ar-H), 1720 (C-O), 1640 ($C=N^+-CH_3$), 1595 (C=C), 1295 and 1125 (C-O 750 and 680 cm^{-1} (pyridinium); ^1H NMR (DMSO-d_6) δ 9.58, 9.27, 8.97, and 8.24 (4H, four m, pyridinium), 5.20-5.65 (1H, broad s, O-CH), 4.47 (3H, s, N^+-CH_3), 1.75 (3H, s, $C=C-CH_3$), 1.30-2.60 (15H).

1-Methyl-3-[2-(3-butenyl)-3-methyl-2-cyclohexenyloxycarbonyl]pyridinium Iodide (2bH)

Yield 83%; IR 3090, 3060, and 3030 (Ar-H). 1722 (C-O), 1647 and 1595 (C=C), 1642 ($C=N^+-CH_3$), 1295 and 1125 (C-O), 920 ($HC=CH_2$), 750 and 680 cm^{-1} (pyridinium); ^1H NMR (DMSO-d_6) δ 9.50, 9.25, 8.95, and 8.21 (4H, four m, pyridinium), 5.82 (1H, m, C=CH), 5.40-5.70 (1H, broad s, O-CH), 4.98 (2H, m, $C=CH_2$), 4.49 (3H, s, N^+-CH_3), 1.71 (3H, s, $C=C-CH_3$), 1.40-2.20 (10H).

1-Methyl-3-[2-(2-methoxyethyl)-3-methyl-2-cyclohexenyloxycarbonyl]pyridinium Iodide (3bH)

Yield 87%; IR 3090, 3060, and 3040 (Ar-H), 1730 (CO-O-C), 1642 ($C=C^+-CH_3$), 1595 (C=C), 1295 and 1125 (C-O), 750 and 680 cm^{-1} (pyridinium); ^1H NMR (DMSO-d_6) δ 9.50, 9.20, 8.95, and 8.25 (4H, four m, pyridinium), 5.18-5.80 (1H, broad s, O-CH), 4.49 (3H, s, N^+-CH_3), 3.39 (2H, t, $O\underline{CH_2}CH_2$), 3.31 (3H, s, OCH_3), 1.74 (3H, s, $C=C-CH_3$), 1.30-2.40 (8H).

Anal. Calcd. (%) for $C_{17}H_{24}INO_3$: C, 48.92; H, 5.80; I, 30.40; N, 3.36
Found (%): C, 48.80; H, 5.91; I, 29.93; N, 3.14

1-Methyl-3-[2-(2-benzyloxyethyl)-3-methyl-2-cyclohexenyloxycarbonyl]pyridinium Iodide (4bH)

Yield 84%; IR 3100, 3070, and 3040 (Ar-H), 1730 (CO-O-C), 1647 ($C=N^+-CH_3$), 1600 (C=C), 1296 and 1125 (C-O), 756 and 670 cm^{-1} (pyridinium); ^1H NMR (DMSO-d_6) δ 9.50, 9.18, 8.92, and 8.25 (4H, four m, pyridinium), 7.31 (5H, s, C_6H_5), 5.30-5.70 (1H, broas s, O-CH), 4.49 (3H, s, N^+-CH_3), 4.42 (2H, s, $\underline{CH_2}Ph$), 3.49 (2H, t, $O\underline{CH_2}CH_2$), 2.40 (2H, t, $OCH_2\underline{CH_2}$), 1.74 (3H, s, $C=C-CH_3$), 1.30-2.50 (6H).

1-Methyl-3-[2-(3-methoxypropyl)-3-methyl-2-cyclohexenyloxycarbonyl]pyridinium Iodide (5bH)

Yield 87%; IR 3090, 3060, and 3040 (Ar-H), 1730 (CO-O-C), 1642 ($C=N^+-CH_3$), 1598 (C=C), 1300 and 1127 (C-O), 755 and 670 cm^{-1} (pyridinium); ^1H NMR (DMSO-d_6) δ 9.50, 9.17, 8.89, and 8.28 (4H, four m, pyridinium), 5.30-5.70 (1H, broad s, O-CH), 4.48 (3H, s, N^+-CH_3), 3.38 (2H, t, $\underline{CH_2}OCH_2$), 3.31 (3H, s, OCH_3), 1.74 (3H, s, $C=C-CH_3$), 1.20-2.50 (10H).

1-Methyl-3-[2-(3-benzyloxypropyl)-3-methyl-2-cyclohexenyloxycarbonyl]pyridinium Iodide (6bH)

Yield 83%; IR 3100, 3060, and 3040 (Ar-H), 1730 (CO-O-C), 1643 ($C=N^+-CH_3$), 1598 (C=C), 1298 and 1125 (C-O), 757 and 670 cm^{-1} (pyridinium); ^1H NMR (DMSO-d_6) δ 9.45, 9.15, 8.88, and 8.25 (4H, four m, pyridinium), 7.30 (5H, s, C_6H_5), 5.30-5.60 (1H, broad s, O-CH), 4.48 (3H, s, N^+-CH_3), 4.44 (2H, s, $\underline{CH_2}Ph$), 3.43 (2H, t, $O\underline{CH_2}CH_2$), 1.72 (3H, s, $C=C-CH_3$), 1.20-2,50 (10H).

2-Butyl-1-deuterio-3-methyl-2-cyclohexenyl nicotinate (1aD), 2-(3-butenyl)--1-deuterio-3-methyl-2-cyclohexenyl nicotinate (2aD), 1-deuterio-2-(2-methoxyethyl)-3-methyl-2-cyclohexenyl nicotinate (3aD), 2-(2-benzyloxyethyl)-1-deuterio--3-methyl-2-cyclohexenyl nicotinate (4aD) 1-deuterio-2-(3-methoxypropyl)-3-methyl--2-cyclohexenyl nicotinate (5aD), 2-(3-benzyloxypropyl)-1-deuterio-3-methyl-2-cyclohexenyl nicotinate (6aD), 1-methyl-3-(2-butyl-1-deuterio-3-methyl-2-cyclohexenyloxycarbonyl)pyridinium iodide (1bD), 1-methyl-3-[2-(3-butenyl)-1-deuterio--3-methyl-2-cyclohexenyloxycarbonyl)]pyridinium iodide (2bD), 1-methyl-3-[1-deuterio-2-(2-methoxyethyl)-3-methyl-2-cyclohexenyloxycarbonyl]pyridinium iodide (3bD), 1-methyl-3-[2-(2-benzyloxyethyl)-1-deuterio-3-methyl-2-cyclohexenyloxycarbonyl]pyridinium iodide (4bD), 1-methyl-3-[1-deuterio-2-(3-methoxypropyl)-3--methyl-2-cyclohexenyloxycarbonyl]pyridinium iodide (5bD) and 1-methyl-3-[2-(3--benzyloxypropyl)-1-deuterio-3-methyl-2-cyclohexenyloxycrbonyl]pyridinium iodide (6bD) gave IR and ^1H NMR spectra fully consistent with their structure. All these compounds had deuterium content >98% d (by ^1H NMR).

KINETIC MEASUREMENTS

Reaction rates were measured by continuous automatic potentiometric titration of the liberate acid[16] by means of a pH-stat (Radiometer, Copenhagen). In each measurement ca. 0.03 mmol of the ester was dissolved in 15 mL of solvent and the liberated acid titrated with 0.025 M NaOH solution in the same solvent.

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